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10/522,341	01/25/2005	Michael Kock	532622010400	5941

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EXAMINER	
ZHENG, LI	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,341	KOCK ET AL.	
	Examiner	Art Unit	
	Li Zheng	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *11-20 and 27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1252005/7252005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-31 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-10 and 21-26, including cytosine deaminase as the marker protein, 5-fluorocytosine as substance X, GenBank Accession No. S56903 and SEQ ID NO: 2 in the reply filed on 4/6/2007 is acknowledged.

Applicants contend that Gleave reference does not teach a method for producing transformed plant cells involving transformation with a nucleotide sequence in combination with a dsRNA or an expression cassette thereof to reduce the expression of the marker protein (response, page 10, 2nd paragraph).

The office contends that claim 1 encompasses any expression cassette, the expression of which would results in reduction of expression of the marker protein. Given the broadest and reasonable interpretation of "reduce", the expression cassette of Gleave does reduce the expression of CodA gene completely by removing it from the genome.

Applicants further contend that Group I-V share a common technical feature relating to transforming a dsRNA sequence or expression cassette thereof to reduce the expression of at least one marker protein, therefore they

should be examined together as having unity of invention (response, page 10, 3rd paragraph).

The office contends that said method does not require introducing the dsRNA to reduce the expression of the marker protein since claim 1 reads on any expression cassette without restriction to a dsRNA sequence or expression cassette thereof. In fact, on page 31 of the specification, Applicants clearly point out that the teaching of Gleave et al. (response, page 10, 2nd paragraph) is one of the preferred embodiments of the invention (specification, page 31, line 21 to page 32, line 2). Therefore, the asserted common technical feature is anticipated by Gleave et al. Furthermore, Groups II and III are only drawn to nucleotide sequences encoding a marker protein or polypeptide of a marker protein, not dsRNA of the marker protein.

Further, Applicants contend that it would not be a serious burden to examine the claims of groups I -V together (response, the paragraph bridging pages 10-11).

The office maintains that the search and examination of all four groups are undue, as each group requires searching for different construct components and analysis of unrelated literatures. In addition, restriction practice by lack of unity does not require the examiner to establish the search burden.

Finally, Applicants contend that all the marker proteins are suitable for practicing the invention and thus share a common property required for action by the invention.

The office maintains that each combination of one species of compounds X together with its corresponding enzyme, genbank accession, or SEQ ID NO has its unique mode of action and therefore is patentably distinguishable from others.

The requirement is still deemed proper and is therefore made FINAL.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See, for example, page 19, line 1 and page 35, line 6.

4. The recitation, "Molecule", on page 23, line 40, is misspelled.

Claim Objections

5. Claim 6 is objected to because Applicants omitted the recitation, --or--, in between part a) and b).

6. Claims 4-6 and 21-24 are objected to because the claims are drawn to non-elected subjected matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-10 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the recitation, "marker protein capable of causing directly or indirectly a toxic effect", renders the claim indefinite. It is unclear what the recitation encompasses. The metes and bounds are not clear.

In claim 1, the recitation, "double-stranded marker protein ribonucleic acid sequence", renders the claim indefinite. It is unclear what the recitation encompasses. The metes and bounds are not clear.

In claim 1, the recitation, "an expression cassette or expression cassettes ensuring expression thereof capable of reducing the expression of at least marker protein", renders the claim indefinite. It is unclear what the recitation encompasses. The recitation reads on any expression cassette that causes suppression of expression of the marker protein. However, part b) suggests that

suppression is due to dsRNA of the gene encoding marker protein. It is unclear what Applicants intend to claim. The metes and bounds are not clear.

In claim 2: the recitation, "capable of converting", renders the claim indefinite. It is unclear what the recitation encompasses. Applicants have not defined the metes and bounds of "capable of converting".

The term "toxic" in claim 2 is a relative term which renders the claim indefinite. The term "toxic" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claims 10 and 26: the recitation, "(preferably non-plant)", in part a) renders the claims indefinite. It is unclear what the recitation intends to limit. The metes and bounds are not clear.

In claims 10 and 26: the recitation, "such as ", in part c), renders the claims indefinite. It is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

In claims 10 and 26:, the recitation, "further comprising", in line 2, renders the claims indefinite. It is unclear whether steps a)-c) are steps in addition to the ones of claim 1 or 2 or not. The metes and bounds are not clear.

Claims 22 and 24 are indefinite for reciting a GenBank Accession No. in the claims. It is unclear what is the sequence given that a sequence can be changed for a given GenBank Accession No. The metes and bounds are not clear.

In claim 26, the recitation, "said nucleic acid sequence", in part e), renders the claim indefinite. It is unclear if the recitation refers to nucleic acid sequence coding for the marker protein or the dsRNA construct. The metes and bounds are not clear.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 7-10, 21, 23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to marker proteins capable of causing directly or indirectly a toxic effect for plant cells and marker proteins capable of converting directly or indirectly a substance X which is nontoxic for said population of plant cells into a substance Y which is toxic for said population .

The Office interprets that the claimed genus encompass any protein causing any toxic effect at any condition or any protein capable of converting any

substance X that is nontoxic for said population of plant at any condition to a substance Y which is toxic for said population at any condition.

The specification teaches that a transgenic plant expressing codA gene was obtained (page 82, lines 24-26). The specification further teaches construction of a binary vector, pSUN1-codA-RNAi-At.Act.-2-At.Als-R-ocsT (SEQ ID NO: 57), comprising dsRNA silencing cassette of codA gene and a herbicide-insensitive variant of the Als gene under the control of the constitutive nitrilase 1 (page 82, lines 29-40). The specification further proposes to transform said transgenic plant with said binary vector and to select the double transgenic plant using selection medium containing 5-fluorocytosine (for reduced codA activity) and the herbicide Pursuit™ (for positive selection marker Als gene)(page 82, line 40-page 83, line 35).

The specification does not describe other species in the claimed genus except for the ones that are listed in claim 4. The claimed genus, however, encompasses any marker protein capable of causing directly or indirectly a toxic effect for plant cells, such as suicidal gene, dominant negative allele of an essential gene etc. The specification fails to correlate the conserved structures of the marker proteins to the function.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of

the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The specification also fails to present representative number of species in the claimed genus. Although the specification present many species in the claimed genus, however, as discussed above, all of those marker proteins belong to one of the subgenera and do not represent other subgenera in claimed genus. Specifically, the only described species are the ones that are listed in claim 4. Therefore, given the breadth of the claim and the lack of enough description, a person skilled in the art would conclude that applicants are not in possession of the claimed genus of marker protein.

Enablement

10. Claims 1-5, 7-10, 21, 23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the CodA marker protein and the dsRNA of CodA, does not reasonably provide enablement for any

marker proteins capable of causing directly or indirectly a toxic effect for plant cells by any means, or any protein capable of converting any substance X that is nontoxic for said population of plant at any condition to a substance Y which is toxic for said population at any condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to marker proteins capable of causing directly or indirectly a toxic effect for plant cells and marker proteins capable of converting directly or indirectly a substance X which is nontoxic for said population of plant cells into a substance Y which is toxic for said population .

The Office interprets that the claimed genus encompass any protein causing any toxic effect at any condition or any protein capable of converting any substance X that is nontoxic for said population of plant at any condition to a substance Y which is toxic for said population at any condition.

The specification teaches that a transgenic plant expressing codA gene was obtained (page 82, lines 24-26). The specification further teaches construction of a binary vector, pSUN1-codA-RNAi-At.Act.-2-At.Als-R-ocsT (SEQ ID NO: 57), comprising dsRNA silencing cassette of codA gene and a herbicide-insensitive variant of the Als gene under the control of the constitutive nitrilase 1 promoter (page 82, lines 29-40). The specification further proposes to transform said transgenic plant with said binary vector and to select the double transgenic plant using selection medium containing 5-fluorocytosine (for reduced codA activity) and the herbicide Pursuit™ (for positive selection marker Als gene)(page 82, line 40-page 83, line 35).

Claim 1 reads on any marker protein capable of causing directly or indirectly a toxic effect for plant cells by any means. The specification does not provide any guidance to practice the invention using marker proteins with completely different modes of action from the one of CodA. For example, the specification does not provide guidance on how to practice the invention without using 5-fluorocytosine. Even for those known genes except for CodA as described in the specification, no guidance or examples are provided in term of whether those genes encoding marker proteins function in plants, or what the concentration of substance X should be used for selection etc. Further, if a plant cell any expressing marker protein which causes any toxic effect at any condition, which results in the death of the plant, it is practically difficult, if possible at all, to obtain such plant cell and use it for practicing the invention. Therefore, in the absence of further guidance, undue experimentation would be

required by one skilled in the art to practice the invention using any marker proteins. See *Genentech Inc. v. Novo Nordisk,* A/S (CA FC) 42 USPQ2d 1001 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Therefore, given the claim breadth, lack of further guidance and additional working example, unpredictability of the art, undue experimentation would be required for a person skilled in the art to practice the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-10 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al. (March 29, 2001, WO 01/21768) in view of Smith et al. (2000, *Nature*, 407:319-320) and Applicants' admitted prior art.

The claims are drawn to a process for preparing transformed plant cells or organisms, comprising: a) transforming a population of plant cells, the cells of said population containing at least one marker protein capable of causing directly or indirectly a toxic effect for said population, with at least one nucleic acid

sequence inserted in combination with at least one double-stranded marker protein ribonucleic acid sequence or an expression cassette or expression cassettes ensuring expression thereof capable of reducing the expression of at least one marker protein, and b) selecting transformed plant cells whose genome contains said nucleic acid sequence and which have a growth advantage over nontransformed cells, due to the action of said double-stranded marker protein ribonucleic acid sequence, from said population of plant cells, the selection being carried out under conditions under which the marker protein can exert its toxic effect on the nontransformed cells; or wherein the marker protein is cytosine deaminases encoded by CodA gene of SEQ ID NO: 2 and substance X is 5-fluorocytosine; or wherein the nucleic acid further comprise a positive selection under the control of a plant promoter; or wherein the plant cell is part of a plant organism or of a tissue, part, organ, cell culture or propagation material derived therefrom; or wherein codA gene is eliminated from the double transgenic plant by crossing to another plant.

Maliga et al. teach that the plant seedling and tissues expressing codA gene from E.coli are sensitive to 5FC and seedlings lacking codA (by deletion due to expression of site-specific recombinase) could be readily identified by 5FC resistance (page 34, lines 17-23).

Maliga et al. does not teaching suppression of codA expression by using dsRNA gene silencing construct targeting codA gene. Maliga et al. also does not teach using positive selection in combination with the negative selection.

Smith et al. teach that a DNA construct that produces hairpin loop type of dsRNA (hpRNA) with functional (i.e. spliceable) intron as spacer enhances silencing efficiency (last two paragraph on left col. of page 320, and also figure 1). Smith et al. also teach that the modifications that help to align the complementary arms of the hairpin and promote the formation of a duplex could increase the efficiency of gene silencing (see last paragraph on the left column of page 320).

In the specification the Applicants disclose that positive (such as npt, hph genes) and negative selection markers (including codA of SEQ ID NO: 2) and compounds used for selections are well known in the art and references are cited (specification , pages 1-3).

Given the recognition of those of ordinary skill in the art of the value of discovering new selection markers for plant transformation, it would have been obvious for a person with ordinary skill in the art to modify the vector expressing site-specific recombinase of Maliga et al. by using the vector expressing dsRNA targeting codA gene as taught by Smith et al. and select double transgenic plant by using 5FU compound of Maliga et al., resulting in the instant inventions. One would have been motivated to do so given the teaching of Maliga et al. that seedlings lacking codA (by deletion due to expression of site-specific recombinase) could be readily identified by 5FC resistance (page 34, lines 17-23), the teaching of Smith et al. that the high percentage of silencing can be achieved by using the hairpin loop structure (Figure 1) and that it is desirable to find alternative selection markers for plant transformation.

It would also have been obvious for a person with ordinary skill in the art to further modify the method by adding an additional positive selection marker as taught by Applicants' own admitted statement of the prior art. One would have been motivated to do so given that the double selection would be more effective to select true transformants.

It would also have been obvious for a person with ordinary skill in the art to further modify the method by eliminating the codA gene from the double transgenic plant by crossing to another plant, given the teaching of Maliga et al. that plastid marker genes in commercial product are undesirable (page 2, line 33-34)

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Zheng whose telephone number is 571-

272-8031. The examiner can normally be reached on Monday through Friday 9:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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